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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/511,515	12/19/2005	Jason Peter Brown	060-004	4660

36844 7590 12/22/2009

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EXAMINER	
LI, QIAN JANICE	
ART UNIT	**PAPER NUMBER**
1633	

NOTIFICATION DATE	DELIVERY MODE
12/22/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/511,515	BROWN, JASON PETER	
	Examiner	Art Unit	
	Q. JANICE LI	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 September 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-33 and 36* is/are pending in the application.

4a) Of the above claim(s) *6,9-17,24,30-33 and 36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7,8,18-23 and 25-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment and remarks filed 9/11/09 are acknowledged. Claims 1, 2, 19-21, 23, 28 have been amended.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the amendment to pending claims and persuasive argument will not be reiterated. The arguments in 9/11/09 response would be addressed to the extent that they apply to current rejection.

Election/Restrictions

Applicant's election with traverse of Group I is acknowledged. The elected invention is drawn to a method for producing antibody using immortalized antibody-secreting cells, and species election drawn to a p53-/- null mouse expressing an oncogene myc under the control of the ecdysone-inducible promoter, wherein expression of myc promotes immortalization.

Claims 1-33, 36 are pending, however, claims 6, 9, 10-14, 15-17, 24, 30-33, 36 are withdrawn from further consideration by the Examiner, pursuant to 37 CFR 1.142(b), as being drawn to non-elected inventions, there being no allowable generic or linking claim. Claims 1-5, 7, 8, 18-23, 25-29 are under current examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-5, 7, 8, 18-23, 25-29 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims are vague and indefinite because of the claim recitation (1, 2), “capable of”, which describes an intrinsic property of the antibody-secreting cells, but the recitation does not require the cells express one or more transgenes. Hence, it is unclear whether it is a limitation.

In the remarks, the applicant argues that the two "capable of" phases are limitations in the context of the claims.

The arguments have been fully considered but found not persuasive. This is because the claims are interpreted given the broadest reasonable interpretation. As such, the step (a) could be reasonably interpreted as providing a transgenic mouse having antibody-secreting cells, wherein the transgene were not necessarily present and expressed in the antibody-secreting cells even though these cells are capable of expressing a transgene. Given the broadest reasonable interpretation, all of the mouse cells are capable of expressing one or more transgenes, and when they do, they are capable of changing to an immortalized state, but it's not a required element of the mouse. According, the rejection stands.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5, 7, 8, 18-21, 23, 25-27, 29 stand rejected under 35 U.S.C. 103(a) as being unpatentable over *Zaccolo et al.* (Int J Clin Res 1993;23:192-8), in view of *Weissinger et al.* (PNAS 1991;88:8735-9, IDS), *Yu et al.* (Oncogene 2002 Mar;21:1922-7) and *Felsher et al.* (Mol Cell 1999;4:199-207).

Claims are directed to a method for producing immortalized antibody-secreting cells via reversible expression of one or more transgene(s), wherein the antibody-secreting cells are obtained from a transgenic animal, and the methods further directed to using the immortalized cells for producing antibodies.

Zaccolo reviews the state of the art with respect to methods of producing antibodies using immortalized cell lines with a focus on improving methodologies for producing immortalized cell lines, humanize antibodies, and obviating the *in vivo* immunization steps, etc. (e.g. the abstract). In the review, two methods of making immortalized antibody-secreting cells were mentioned, i.e. fusion of immune spleen lymphocytes with a suitable non-secreting myeloma partner, and immortalizing cells by EB virus infection (see e.g. column 1, page 193). *Zaccolo* teaches advantages and disadvantages of each technique (such as instability and low level of Ig production), and implicitly pointed to the need to further improve the immortalization process. *Zaccolo* does not teach using transgenic animals or oncogenes for preparing immortalized antibody-secreting cells.

Weissinger supplemented *Zaccolo* by establishing further development in the pertinent art using oncogene expression for direct immortalization of antibody-secreting B lymphocytes. *Weissinger* infected immunized mouse with a replication-defective retrovirus co-expressing oncogene v-*abl* and c-*myc*, and reports the virus rapidly induced plasmacytomas (tumors of antibody-secreting cells) in 100% of adult balb/c mice. *Weissinger* also reports the concentration, specificity and affinity of the antibodies produced by the plasmacytomas were comparable to monoclonal antibodies obtained with conventional hybridoma technology, and secreted IgG, IgM, and IgA antibodies (e.g. the abstract). *Weissinger* concluded "TO DATE, ALL ABL-MYC-INDUCED PLASMACYTOMAS HAVE BEEN VERY STABLE *IN VIVO* AND *IN VITRO*" and "THE USE OF THIS VIRUS MAY PROVE TO BE A VALUABLE ALTERNATIVE TO THE CONVENTIONAL HYBRIDOMA TECHNIQUE FOR PRODUCTION OF MONOCLONAL ANTIBODIES" (the paragraph bridging columns 1 & 2, page 8739).

Yu supplemented *Zaccolo* in view of *Weissinger* by establishing it was well known in the art using a transgenic mouse for directly immortalizing B lymphocytes. *Yu* reports obtaining bone marrow progenitor cells from p53 null mouse and transfecting the cells with the *myc* gene. *Yu* concluded "INACTIVATION OF P53 AND OVEREXPRESSION OF MYC IS ALL THAT IS NECESSARY FOR THE DEVELOPMENT OF FULL-FLEDGED B-LYMPHOMAS" (=plasmacytomas in the mouse). *Yu* does not use a conditional/reversible immortalization regimen.

Felsher supplemented the deficiency by establishing using an inducible expression system controlling the expression of the *myc* gene for reversible

tumorigenesis was known in the art. *Felsher* applied a tetracycline regulatory system to generate transgenic mice that conditionally express the *myc* oncogene in hematopoietic cells, wherein the oncogene could be turned on and off in the presence or absence of a chemical stimulus (tet).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method taught by *Zaccolo* in view of *Weissinger* for preparing immortalized antibody-secreting cells using the method as taught by *Yu* and *Felsher* with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because the need for improved methods of immortalization as taught by *Zaccolo* in view of *Weissinger*. Given all the recited elements were known in the art for making instantly claimed transgenic mouse and antibody-secreting cells, "THE COMBINATION OF FAMILIAR ELEMENTS ACCORDING TO KNOWN METHODS IS LIKELY TO BE OBVIOUS WHEN IT DOES NO MORE THAN YIELD PREDICTABLE RESULTS." *KSR,* 127 S. Ct. at 1740, 82 USPQ2d at 1395-96. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

In the remarks, the applicant highlighted that the knowledge disclosed by Zaccolo reviewing the state of the art in 1993, while Yu and Felsher are directed to a completely different field of technology. The applicant asserted there is nothing in Zaccolo or Weissinger which would lead the person of ordinary skill to Yu and Felsher and there is nothing in Yu and Felsher regarding antibody production which would allow the person of ordinary skill to identify the documents.

Applicant's arguments have been fully considered but they are not persuasive. In response to applicant's argument that cited reference is nonanalogous art, it has been held that a prior art reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the applicant was concerned, in order to be relied upon as a basis for rejection of the claimed invention. See *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). In this case,

producing antibodies using immortalized cells and investigation of oncogene tumorogenesis were two independent fields of scientific endeavor. However, the teaching of *Weissinger* establishes that the skilled in the art had linked the two fields by expressing oncogenes for immortalizing antibody-producing cells. Thus, expressing an oncogene in an antibody-producing B lymphocytes was reasonably pertinent to the particular problem with which the applicant was concerned.

Apparently as early as 1993, producing antibodies using immortalized antibody-producing cells had been known, and the need for further improvement of the technique had also been known as taught by *Zaccolo. Weissinger* supplemented *Zaccolo* by establishing it was known in the art that one strategy to immortalize antibody-producing cells was oncogene expression for direct immortalization of antibody-secreting B lymphocytes. *Weissinger* clearly concluded "TO DATE, ALL ABL-MYC-INDUCED PLASMACYTOMAS HAVE BEEN VERY STABLE *IN VIVO* AND *IN VITRO*" and "THE USE OF THIS VIRUS MAY PROVE TO BE A VALUABLE ALTERNATIVE TO THE CONVENTIONAL HYBRIDOMA TECHNIQUE FOR PRODUCTION OF MONOCLONAL ANTIBODIES" (the paragraph bridging columns 1 & 2, page 8739). As such, the two fields had been tied together by the skilled in the art long before instant filing date. The Supreme Court stated "IF A TECHNIQUE HAS BEEN USED TO IMPROVE ONE DEVICE, AND A PERSON OF ORDINARY SKILL IN THE ART WOULD RECOGNIZE THAT IT WOULD IMPROVE SIMILAR DEVICES IN THE SAME WAY, USING THE TECHNIQUE IS OBVIOUS UNLESS ITS ACTURAL APPLICATION IS BEYOND THAT PERSON'S SKILL" (*KSR Int'l Co. v. Teleflex Inc.,* 127 S. Ct. at 1740, 82 USPQ2d at 1395-96, see particular page 4 of Syllabus). Since oncogene expression had been used for immortalizing antibody-producing cells, one would have continued interests to look for newer knowledge available in the field of oncology for

improving technique of immortalizing antibody-producing cells and finding the documents of *Yu* and *Felsher*. The court has determined that the motivation to combine may be found in the nature of the problem to be solved. "FINDING OF OBVIOUSNESS DOES NOT REQUIRE EXISTENCE OF EXPRESS, WRITTEN MOTIVATION TO COMBINE IN PRIOR ART, SINCE MOTIVATION TO COMBINE MAY BE FOUND IN NATURE OF PROBLEM TO BE SOLVED, LEADING INVENTORS TO LOOK TO REFERENCES RELATING TO POSSIBLE SOLUTIONS TO THAT PROBLEM". (*Ruiz v. A.B. Chance Co.*, 69 USPQ2d 1686 CA FC 2004). Since the *Yu* reference reflects the further development in the field of oncology showing the combination of a p53-/- cell expressing myc oncogene would lead to immortalization (tumor formation) of the antibody-producing cells (B-cell), it would suggested to those intending to immortalizing antibody producing cells to take the same approach. *Yu* reference also provides a reasonable expectation of success when combining the transgenic p53-/- mouse with the myc oncogene expression for immortalizing B-lymphocytes (antibody-producing cells).

Felsher was cited to show an inducible expression system controlling the expression of the *myc* gene for reversible tumorigenesis was known in the art, which is completely relevant in both immotalization of antibody-producing cell and investigation of tumorogenesis.

In view of above considerations, it appears all the recited elements were known in the art, and hence "the combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR,* 127 S. Ct. at 1740, 82 USPQ2d at 1395-96.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Accordingly, the rejection stands for reasons or record and *supra*.

Claim 22 stands rejected under 35 U.S.C. 103(a) as being unpatentable over *Zaccolo et al*. (Int J Clin Res 1993;23:192-8), in view of *Weissinger et al*. (PNAS 1991;88:8735-9, IDS), *Yu et al*. (Oncogene 2002 Mar;21:1922-7), and *Felsher et al.* (Mol Cell 1999;4:199-207) as applied to claims 1-5, 7, 8, 18-21, 23, 25-27, 29 above, further in view of *Irsch et al*. (Immunotechnol 1995;1:115-25), for reasons of record and *supra*.

Claim 25 stands rejected under 35 U.S.C. 103(a) as being unpatentable over *Zaccolo et al*. (Int J Clin Res 1993;23:192-8), in view of *Weissinger et al*. (PNAS 1991;88:8735-9, IDS), *Yu et al*. (Oncogene 2002 Mar;21:1922-7), and *Felsher et al.* (Mol Cell 1999;4:199-207) as applied to claims 1-5, 7, 8, 18-21, 23, 25-27, 29 above, further in view of *No et al*. (PNAS 1996;93:3346-51), for reasons of record and *supra*.

Claim 28 stands rejected under 35 U.S.C. 103(a) as being unpatentable over *Zaccolo et al*. (Int J Clin Res 1993;23:192-8), in view of *Weissinger et al*. (PNAS 1991;88:8735-9, IDS), *Yu et al*. (Oncogene 2002 Mar;21:1922-7), and *Felsher et al.* (Mol Cell 1999;4:199-207) as applied to claims 1-5, 7, 8, 18-21, 23, 25-27, 29 above, further in view of *Yokoyama* (Curr Protoc Immunol 2001;Appendix 3G), for reasons of record and *supra*.

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. JANICE LI** whose telephone number is **571-272-**

0730. The examiner can normally be reached on 9 AM -7:00pm, Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The **fax** numbers for the organization where this application or proceeding is assigned are **571-273-8300**.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

For all other customer support, please call the USPTO Call Center (UCC) at **800-786-9199**.

/Q. JANICE LI, M.D./
Primary Examiner, Art Unit 1633

QL
December 18, 2009